

Recent Advances in Synthesis of Thiazoles ring: Mini Review

Poonam

Assistant Professor in Chemistry, Dr. B.R.A. Govt. College, Kaithal

DOI: <https://doi.org/10.70388/ijabs250173>

Received on Nov 06, 2025

Accepted on Dec 15, 2025

Published on Jan 15, 2026

This article is licensed under a
license [Commons Attribution-
Non-commercial-No
Derivatives 4.0 International
Public License \(CC BY-NC-ND](#)

Introduction

Thiazoles are a class of five-membered heterocyclic compounds containing both sulfur and nitrogen atoms in the ring, specifically at the 1st and 3rd positions. The simplest member of this family is thiazole (C_3H_3NS). These compounds exhibit aromatic character, owing to a delocalized six π -electron system that follows Hückel's rule ($4n + 2$ rule).

The presence of two heteroatoms (S and N) gives thiazoles distinctive chemical reactivity, electron distribution, and biological activity compared to other heterocycles such as pyrrole, furan, and thiophene. The ring is planar, aromatic, and relatively stable, yet can undergo electrophilic and nucleophilic substitutions at specific positions (mainly C-5 and C-2).

Thiazoles are widely distributed in nature and are found as essential components in many biologically important molecules, such as thiamine (vitamin B_1), which plays a vital role in carbohydrate metabolism. Many synthetic thiazole derivatives show a broad range of pharmacological activities, including antibacterial, antifungal, anti-inflammatory, anticancer, and antiviral properties.

In addition to their biological roles, thiazole rings are also valuable in industrial and materials chemistry, serving as intermediates in organic synthesis, components of dyes, and building blocks for pharmaceuticals and polymers. Because of their stability, versatility, and biological

importance, thiazoles continue to attract significant interest in medicinal chemistry and synthetic organic research.

Structure and Aromaticity of Thiazoles

1. Structure

Thiazoles are five-membered heterocyclic compounds containing one sulfur atom and one nitrogen atom at the 1 and 3 positions, respectively. The parent compound is 1,3-thiazole with the molecular formula C_3H_3NS .

Structural features:

- The ring contains three carbon atoms, one nitrogen, and one sulfur.
- The nitrogen atom is sp^2 hybridized, contributing one lone pair to the aromatic π -system.
- The sulfur atom also contributes one lone pair to the delocalized π -system, while its second lone pair remain localized.
- The ring is planar, ensuring effective overlap of p-orbitals and π -electron delocalization.

Bond character:

- Thiazoles have partial double-bond character between C–N, C–S, and C–C bonds due to delocalization.
- The presence of two heteroatoms leads to unequal electron density distribution, making some carbon atoms more electron-deficient than others (especially C-2).

2. Aromaticity

Thiazole is aromatic because it satisfies **Hückel's rule** for aromaticity ($4n + 2$ π -electrons, where $n = 1$).

- The ring has 6 π -electrons in total:
 - Four π -electrons from the two C=C bonds.
 - Two π -electrons from the lone pair of the nitrogen atom.

- The sulfur atom retains one lone pair outside the π -system.

Key points about aromaticity:

- The ring is planar, allowing continuous overlap of p-orbitals.
- Delocalization of π -electrons over the entire ring gives extra stability.
- The aromaticity makes thiazole chemically stable and resistant to addition reactions.
- Due to the presence of both electron-withdrawing (N) and electron-donating (S) atoms, the ring shows polarization, giving it a dipole moment (~ 1.6 D).

3. Consequences of Structure and Aromaticity

- The C-2 position is electron-deficient $\rightarrow$ susceptible to nucleophilic attack.
- The C-5 position is relatively electron-rich $\rightarrow$ undergoes electrophilic substitution.
- The aromatic ring contributes to biological stability and ligand binding in thiazole-containing drugs.

Synthesis of Thiazoles

Thiazoles can be synthesized by several methods, both classical and modern, depending on the desired substitution pattern. The most widely used methods involve the cyclization of precursors containing sulfur and nitrogen atoms with carbonyl compounds or α -haloketones.

1. Hantzsch Thiazole Synthesis (Classical Method)

The **Hantzsch synthesis (1887)** is the most common and convenient method for preparing substituted thiazoles.

Reactants:

- α -Haloketone or α -haloaldehyde
- Thioamide or thiourea

General Reaction:

α - Haloketone + Thioamide $\xrightarrow{\text{Ethanol or Acetic acid}}$ Thiazole derivative + HX

Example:

Mechanism (Simplified):

1. Nucleophilic attack of the thioamide sulfur on the α -haloketone carbon $\rightarrow$ intermediate formation.
2. Intramolecular cyclization via attack of the nitrogen on the carbonyl carbon.
3. Dehydration gives the thiazole ring.

Advantages:

1. Simple, versatile, and yields are usually good.
2. Applicable to a wide range of substituents.

2. Gabriel–Coulomb Synthesis

In this method, α -halocarbonyl compounds react with thioamides under basic conditions.

General Reaction:



This reaction is very similar to the Hantzsch method but is typically carried out in basic media to enhance nucleophilicity.

3. From α -Acylaminoketones

Thiazoles can also be synthesized from α -acylaminoketones by cyclization using sulfurizing agents such as phosphorus pentasulfide (P_2S_5) or Lawesson's reagent.

Reaction:

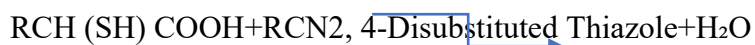


This method is useful for synthesizing 2, 4-disubstituted thiazoles.

4. From Dithioacids and Nitriles

Condensation of α -dithio acids ($\text{RCH}(\text{SH})\text{COOH}$) with nitriles (RCN) under heating gives 2, 4-disubstituted thiazoles.

Reaction:



This method is often used for preparing thiazoles with complex substituents.

5. Modern / Green Synthetic Approaches

To make thiazole synthesis more efficient and environmentally friendly, several modern techniques have been developed:

- **Microwave-assisted synthesis** — reduces reaction time and improves yield.
- **Solvent-free synthesis** — avoids toxic solvents and simplifies purification.
- **Ionic liquid catalysis** — enhances reaction rate and recyclability.
- **One-pot multicomponent reactions** — combine multiple reagents in a single step for rapid library synthesis of thiazole derivatives.

Chemical Properties of Thiazoles

Thiazoles are aromatic heterocyclic compounds that exhibit characteristic chemical reactivity due to the presence of both nitrogen and sulfur atoms in the ring. Their reactions are influenced by the electron distribution within the ring — the nitrogen atom is electron-withdrawing, while the sulfur atom is weakly electron-donating, leading to polarization of the ring.

1. Aromatic Character and Stability

- Thiazoles are **aromatic**, satisfying **Hückel's rule (6 π -electrons)**.
- The ring is planar and stable toward addition reactions that would disrupt aromaticity.
- They resist hydrogenation and oxidation under mild conditions, confirming their aromatic nature.

2. Electrophilic Substitution Reactions

Thiazoles undergo electrophilic substitution reactions, but less readily than benzene because the ring is electron-deficient.

Reactivity order:



The **C-5 position** is the most electron-rich site (due to resonance), hence electrophiles attack there preferentially.

Examples:

- **Nitration:** Thiazole $\rightarrow$ 5-Nitrothiazole (using $\text{HNO}_3/\text{H}_2\text{SO}_4$)
- **Sulfonation:** Thiazole $\rightarrow$ 5-Sulfonic acid derivative
- **Halogenation:** Thiazole + $\text{Br}_2 \rightarrow$ 2-Bromothiazole or 5-Bromothiazole (depending on conditions)

Note: Electrophilic substitution occurs mainly at **C-5**, not at C-2 (which is electron-poor).

3. Nucleophilic Substitution Reactions

The C-2 position is electron-deficient due to the adjacent nitrogen atom, making it susceptible to nucleophilic attack.

Example:



This type of reaction is important for synthesizing pharmacologically active derivatives.

4. Addition Reactions (Rare)

Because thiazoles are aromatic, they generally resist addition reactions. However, under strong reducing conditions, addition across the double bonds can occur, leading to dihydrothiazole derivatives.

5. Ring Cleavage Reactions

Thiazoles can undergo ring-opening reactions when treated with strong nucleophiles or oxidizing agents.

Examples:

- Treatment with alkali or acidic hydrolysis → opens the ring to form amino acids or dithio derivatives.
- Oxidation with H_2O_2 or peracids → forms sulfoxides or sulfones.

6. Metalation and Lithiation

At low temperatures, thiazoles can be metalated at the C-2 position using strong bases like n-butyllithium (n-BuLi).

Thiazole+n-BuLi→2-Lithiothiazole

The lithiated intermediate can then react with electrophiles (e.g., carbonyl compounds, alkyl halides) to form 2-substituted thiazoles.

7. Reduction and Oxidation

- **Reduction:** Thiazoles are resistant to mild reduction but can be reduced under strong conditions to form dihydrothiazoles.
- **Oxidation:** Sulfur atom can be oxidized to give thiazole S-oxide or S-dioxide using oxidizing agents like H_2O_2 or KMnO_4 .

8. Coordination and Complex Formation

The nitrogen atom in thiazole acts as a Lewis base and can coordinate to metal ions, forming metal–thiazole complexes. These complexes are often used in catalysis and coordination chemistry.

Industrial and Analytical Applications of Thiazoles

Thiazoles and their derivatives play a significant role in various industrial, pharmaceutical, and analytical fields. Their unique aromatic heterocyclic structure — containing both sulfur and nitrogen atoms — imparts chemical stability, reactivity, and biological activity, making them valuable in numerous applications.

1. Pharmaceutical Industry

Thiazole derivatives form an essential structural unit in many clinically important drugs because of their wide range of biological activities.

Applications:

- **Antibacterial and Antifungal Agents:** Examples include Sulfathiazole, Cephazolin, and Thiabendazole.
- **Anti-inflammatory and Analgesic Drugs:** Meloxicam and Fanutizole contain thiazole rings that enhance COX inhibition.
- **Anticancer Agents:** Thiazole-based compounds such as Dasatinib and Tiazofurin act as kinase inhibitors.
- **Vitamin Component:** The thiazole ring is a key part of thiamine (vitamin B₁), essential for carbohydrate metabolism.
- **Antiviral and Antitubercular Agents:** Many thiazole derivatives show strong activity against viruses and *Mycobacterium tuberculosis*.

Significance:

The thiazole nucleus contributes to lipophilicity, metabolic stability, and receptor binding, making it a valuable pharmacophore in drug design.

2. Dye and Pigment Industry

Thiazole derivatives are used in the synthesis of dyes, pigments, and optical brighteners because of their strong chromophoric properties and stability to light and heat.

Examples:

- **Thiazole orange** — a fluorescent dye used in DNA and RNA staining.

- **Thioflavin T** — used for amyloid detection in biological research.
- **Thiazolyl azo dyes** — used in textiles and printing due to their bright color and fastness.

3. Polymer and Material Science

Thiazole-containing polymers exhibit electronic, photophysical, and mechanical properties, making them useful in:

- Conductive and semiconductive materials
- Organic light-emitting diodes (OLEDs)
- Solar cells
- Sensors and nanomaterials

Example:

Thiazole-based copolymers are used in **optoelectronic devices** due to their high charge mobility and stability.

4. Agrochemical Industry

Thiazole derivatives are key components in pesticides, herbicides, and fungicides due to their bioactivity and stability.

Examples:

- **Thiabendazole** — a fungicide used to protect fruits and vegetables.
- **Thiamethoxam** — a thiazole-based insecticide belonging to the neonicotinoid class.
- **Sulfenazole derivatives** — used as herbicides.

5. Analytical Chemistry Applications

Thiazole derivatives are useful in analytical and diagnostic chemistry due to their ability to form colored or fluorescent complexes.

Applications:

- **Fluorescent probes and indicators:** Thiazole dyes (like Thiazole *orange*) are used for nucleic acid quantification in gel electrophoresis and flow cytometry.
- **Spectrophotometric and fluorometric assays:** Thiazole derivatives act as chromogenic reagents for detecting trace metals or biomolecules.
- **pH and metal ion sensors:** Thiazole-based ligands exhibit fluorescence changes upon binding to specific ions (e.g., Cu^{2+} , Zn^{2+}).

6. Chemical and Synthetic Uses

- Serve as building blocks or intermediates in the synthesis of:
 - Pharmaceuticals
 - Agrochemicals
 - Fine chemicals and heterocyclic compounds
- Used as ligands in coordination chemistry due to the presence of a nitrogen donor atom.

7. Biochemical and Research Applications

- Thiazole derivatives (like thiazole orange and thioflavin T) are used in biomolecular research for studying DNA/RNA binding, protein folding, and amyloid fibril formation.
- Thiazole-tagged molecules are used as fluorescent labels and molecular probes.

Challenges & future directions

- While many promising thiazole derivatives show in-vitro activity, fewer have progressed to in-vivo evaluation or advanced preclinical/clinical stages.
- Selectivity, toxicity, metabolic stability remains key hurdles for therapeutic thiazoles.
- For material applications, translation to scalable, cost-effective manufacturing remains non-trivial.
- More detailed mechanistic understanding (e.g., binding modes, off-target effects) is needed to optimize leads.
- Given the broad potential, cross-disciplinary integration (medicinal chemistry + materials science + computational design) will likely accelerate future advances.

References:

1. Ahmad, M. R., & Ahmad, A. H. (2014). Synthesis and characterization of some new derivatives from 2-mercaptobenzothiazole, Iraqi. *Journal of Science*, 55, 319–333.
2. Bondock, S., Naser, T., & Ammar, Y. A. (2013). Synthesis of some new 2-(3-pyridyl)-4,5-disubstituted thiazoles as potent antimicrobial agents. *European Journal of Medicinal Chemistry*, 62, 270–279. <https://doi.org/10.1016/j.ejmech.2012.12.050>
3. Franchini, C., Muraglia, M., Corbo, F., Florio, M. A., Di Mola, A., Rosato, A., Matucci, R., Nesi, M., van Bambeke, F., & Vitali, C. (2009). Synthesis and biological evaluation of 2-mercapto-1,3-benzothiazole derivatives with potential antimicrobial activity. *Archiv der Pharmazie, Chemistry in Life Sciences*, 342(10), 605–613. <https://doi.org/10.1002/ardp.200900092>
4. Gomha, S. M., Salaheldin, T. A., Hassaneen, H. M. E., Abdel-Aziz, H. M., & Khedr, M. A. (2015). Synthesis, characterization and molecular docking of novel bioactive thiazolyl-thiazole derivatives as promising cytotoxic antitumor drug. *Molecules*, 21(1), Article E3. <https://doi.org/10.3390/molecules21010003>
5. Lv, P.-C., Wang, K.-R., Yang, Y., Mao, W.-J., Chen, J., Xiong, J., & Zhu, H.-L. (2009). Design, synthesis and biological evaluation of novel thiazole derivatives as potent FabH inhibitors. *Bioorganic and Medicinal Chemistry Letters*, 19(23), 6750–6754. <https://doi.org/10.1016/j.bmcl.2009.09.111>
6. Onigo, S., Duma, M., Oniga, O., Tiperciuc, B., Piranau, A., Araniciu, C., & Palage, M. (2015). Synthesis of some new 4-methyl-2-(4-pyridyl)-thiazole-5-yl-azoles as potential antimicrobial agents. *Farmacia*, 63, 171–178.
7. Rahim, F., Ullah, H., Javid, M. T., Wadood, A., Taha, M., Ashraf, M., Shaukat, A., Junaid, M., Hussain, S., Rehman, W., Mehmood, R., Sajid, M., Khan, M. N., & Khan, K. M. (2015). Synthesis, in vitro evaluation and molecular docking studies of thiazole derivatives as new inhibitors of α -glucosidase. *Bioorganic Chemistry*, 62, 15–21. <https://doi.org/10.1016/j.bioorg.2015.06.006>
8. Raju, G. N., Karumudi, B. S., & Rao, N. R. (2017). Benzothiazole—Versatile heterocyclic nucleus in medicinal chemistry: A review. *International Journal of Pharmaceutical Chemistry*, 14, 729–742.

9. Reddy, G. M., Garcia, J. R., Reddy, V. H., de Andrade, A. M., Camilo, A., Jr., Pontes Ribeiro, R. A., & de Lazaro, S. R. (2016). Synthesis, antimicrobial activity and advances in structure–activity relationships (SARs) of novel tri-substituted thiazole derivatives. *European Journal of Medicinal Chemistry*, 123, 508–513. <https://doi.org/10.1016/j.ejmech.2016.07.062>
10. Garima, G., & Bhukkal, S. (2025b). An approach towards the fabrication of flexible piezoelectric composite film of CA-Doped ZNO/PVDF for energy harvesting application. *International Journal of Applied and Behavioral Sciences*, 2(01), 28–42. <https://doi.org/10.70388/ijabs250104>